SUMMARY BASIS OF APPROVAL

1.0 GENERAL INFORMATION

Licensed Product Name:	Immune Globulin Intravenous (Human), 10%
Proprietary Product Name:	GAMMAGARD LIQUID
Other Name:	Not Applicable
Name and Address of Sponsor:	Baxter Healthcare Corporation One Baxter Way Westlake Village, California 91362
Biologics License Application Tracking Number:	STN 125105.0
Date of Submission:	29 June 2004

2.0 INDICATIONS FOR USE

GAMMAGARD LIQUID is indicated for the treatment of primary immunodeficiency disorders associated with defects in humoral immunity. These include but are not limited to congenital X-linked agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

3.0 DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

A. Dosage Form

GAMMAGARD LIQUID is a ready-for-use sterile, liquid preparation of highly purified and concentrated immunoglobulin G (IgG) antibodies.

The distribution of the IgG subclasses is similar to that of normal plasma. The Fc and Fab functions are maintained in GAMMAGARD LIQUID. Pre-kallikrein activator activity is not detectable. GAMMAGARD LIQUID contains 100 mg/mL protein. At least 98% of the protein is gammaglobulin, the immunoglobulin A (IgA) is present in trace amounts with an average of 37 μg/mL, and

immunoglobulin M is present in trace amounts. GAMMAGARD LIQUID contains a broad spectrum of IgG antibodies against bacterial and viral agents. Glycine (0.25M) serves as a stabilizing and buffering agent, and there are no added sugars, sodium or preservatives. The pH is 4.6 to 5.1[1]. The osmolality is 240-300 mOsmol/kg, which is similar to physiological osmolality (285 to 295 mOsmol/kg).

B. Route of Administration

GAMMAGARD LIQUID should only be administered intravenously. Other routes of administration have not been evaluated.

GAMMAGARD LIQUID should be at room temperature during administration.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use if particulate matter and/or discoloration is observed. Only clear or slightly opalescent and colorless or pale yellow solutions are to be administered.

C. Recommended Dosage

For patients with Primary Immunodeficiency, monthly doses of approximately 300 – 600 mg/kg infused at 3 to 4 week intervals are commonly used. As there are significant differences in the half-life of IgG among patients with Primary Immunodeficiency, the frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper amount can be determined by monitoring clinical response. The minimum serum concentration of IgG necessary for protection varies among patients and has not been established by controlled clinical studies.

4.0 MANUFACTURING, CHEMISTRY AND CONTROLS

A. Manufacturing Process Overview

The GAMMAGARD LIQUID manufacturing process employs a modified Cohn-Oncley cold alcohol fractionation procedure to isolate an intermediate immunoglobulin G (IgG) fraction, referred to as Precipitate G, from human plasma pools. ----------
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---------- Precipitate G is further purified by a continuous process through the use of weak cation exchange chromatography (CM Sepharose Fast Flow) and weak anion exchange chromatography (ANX Sepharose 4 Fast Flow, low substitution) to final formulation. Three dedicated virus reduction steps are included in the downstream purification of Precipitate G, which are solvent/detergent (S/D) treatment, nanofiltration, and incubation at low pH and elevated temperature in the final formulation. The final formulation step is achieved at the ultra/diafiltration step against 0.25 M glycine buffer at pH 4.2 to meet the final release criteria of an osmolality of 240 to 300 mOsmol/kg, a pH of 4.6 to 5.1[1], and a protein concentration of human IgG of 9.0 to 11.0%.

B. Methods Validation

The test parameters, test methods and release specifications for GAMMAGARD LIQUID are provided in Table 1. The specifications have been set in accordance with pharmacopoeia requirements as well as based on the analysis of the product manufactured in support of this project.

1 pH is measured after the solution is diluted to 1% protein with saline. The pH range of 4.6 to 5.1 corresponds to a range of 4.4 to 4.9 when the solution is measured undiluted.

Table 1 Final Product Release Specifications for GAMMAGARD LIQUID		
Test Parameter	**Test Method**	**Specification**
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Appearance	Visual Inspection	The liquid preparation is clear or slightly opalescent and colorless or pale yellow.
Diphtheria Antibody	Neutralization	NLT ---U of US Standard Antitoxin/mL
Glycine	----------	----------
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IgA	----------	----------
IgM	----------	----------
Measles Antibody	----------	NLT ---times the antibody level of NIH Reference Measles Immune Globulin Lot ----
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Osmolality	----------	240 – 300 mOsmol/kg
pH (diluted)	----------	4.6 – 5.1
Poliomyelitis Antibody	Neutralization	NLT ------times the antibody level of NIH Reference Polio Immune Globulin Lot ----
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Prekallikrein Activator Activity	----------	----------
Protein Identity	----------	Human Protein: Positive
Purity	----------	Purity (gamma globulin): 98% minimum
Pyrogen	USP Method	Rabbit Test Dose--mL/kg Satisfactory
Safety Test	USP Method	Satisfactory
Sterility	----------	Satisfactory
Total Protein	----------	----------
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EP = European Pharmacopoeia

NIH = National Institute of Health
CBER = Center for Biologics Evaluation and Research
PKA = Prekallikrein Activator
USP = United States Pharmacopoeia
NLT= Not less than

GAMMAGARD LIQUID conformance lots were manufactured to validate the processes at Baxter Los Angeles, California, Vienna, Austria and Lessines, Belgium commercial scale facilities. Upstream processing to obtain the intermediate, Precipitate G, was performed in the Los Angeles and Vienna facilities. Precipitate G lots were shipped to the Baxter Lessines facility for downstream processing to final container lots.

Process validation was performed during the manufacture of Precipitate G and GAMMAGARD LIQUID to demonstrate the following:

Precipitate G

- A controlled and robust manufacturing process
- Capability of the process to manufacture Precipitate G consistently meeting pre-determined specifications
- Capability of the process to manufacture Precipitate G consistently demonstrated with additional product characterization
- The specified range of starting plasma volumes do not affect the process capability and product characteristics

GAMMAGARD LIQUID Final Container

- A controlled and robust manufacturing process
- Capability of the process to manufacture GAMMAGARD LIQUID consistently from Precipitate G meeting pre-determined specifications
- Capability of the process to manufacture GAMMAGARD LIQUID consistently demonstrated with additional product characterization
- Capability to remove process-related impurities through the manufacturing process
- Capability of the process to manufacture GAMMAGARD LIQUID using two different quantities of Precipitate G

C. Validation of Viral Safety

In vitro virus spiking studies have been used to validate the capability of the manufacturing process to inactivate and remove viruses. To establish the minimum applicable virus clearance capacity of the manufacturing process, these virus clearance studies were performed under extreme conditions (e.g., at minimum S/D concentrations, incubation time and temperature for the S/D treatment). Virus clearance studies for GAMMAGARD LIQUID performed in accordance with good laboratory practices (Table 2) have demonstrated that:

- S/D treatment inactivates the lipid-enveloped viruses investigated to below detection limits within minutes.

- 35 nm nanofiltration removes lipid-enveloped viruses to below detection limits and reduces the non-lipid enveloped viruses HAV and B19V. As determined by a polymerase chain reaction assay, nanofiltration reduced B19V by a mean $\log_{10}$ reduction factor of 4.8 genome equivalents.

- Treatment with low pH at elevated temperature of 30°C to 32°C inactivates lipid-enveloped viruses and encephalomyocarditis virus (EMCV, model for HAV) to below detection limits, and reduces mice minute virus (MMV, model for B19V).

Table 2 Three Dedicated Independent Virus Inactivation/Removal Steps Mean Log_{10} Reduction Factors [a] (RFs) For Each Virus and Manufacturing Step							
Virus type	**Enveloped RNA**			**Enveloped DNA**	**Non-enveloped RNA**		**Non-enveloped DNA**
Family	**Retroviridae**	**Flaviviridae**		**Herpesviridae**	**Picornaviridae**		**Parvoviridae**
Virus	**HIV-1**	**BVDV**	**WNV**	**PRV**	**HAV**	**EMCV**	**MMV**
SD treatment	>4.5	>6.2	n.a.	>4.8	n.d.	n.d.	n.d
35 nm nanofiltration	>4.5	>5.1	>6.2	>5.6	5.7	1.4	2.0
Low pH treatment	>5.8	>5.5	>6.0	>6.5	n.d. [b]	>6.3	3.1
Overall log reduction factor (ORF)	**>14.8**	**>16.8**	**>12.2**	**>16.9**	**5.7** [b]	**>7.7**	**5.1**

Abbreviations: HIV-1, Human Immunodeficiency Virus Type 1; BVDV, Bovine Viral Diarrhea Virus (model for Hepatitis C Virus and other lipid enveloped RNA viruses); WNV, West Nile Virus; PRV, Pseudorabies Virus (model for lipid enveloped DNA viruses, including Hepatitis B Virus); EMCV, Encephalomyocarditis Virus (model for non-lipid enveloped RNA viruses, including Hepatitis A virus [HAV]); MMV, Mice Minute Virus (model for non-lipid enveloped DNA viruses, including B19 virus [B19V]); n.d. (not done), n.a. (not applicable).

[a] For the calculation of these RF data from virus clearance study reports, applicable manufacturing conditions were used. Log_{10} RFs on the order of 4 or more are considered effective for virus clearance in accordance with the Committee for Medicinal Products for Human Use (CHMP, formerly CPMP) guidelines.

[b] No RF obtained due to immediate neutralization of HAV by the anti-HAV antibodies present in the product.

D. Stability Studies

Evaluation of stability of the GAMMAGARD LIQUID final product was performed. Final container lots have been stored and evaluation for 42 months at +5°C has been initiated. Samples have also been stored at +25°C and +30°C to evaluate stability under room temperature storage conditions. Samples at the proposed storage temperatures are tested at 3-month intervals followed by 6-month and 12-month intervals according to the ICH Harmonized Tripartite Guideline, Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products, 1995.

Interim real time stability data are available for six manufacturing scale clinical lots. Thirty-six months test results for one lot, 30 months test results for two lots, and 24 months test results for three lots are currently available. All data are satisfactory and within specifications when stored at temperatures of +5°C and +25°C. Currently, 9 months data (8 lots) and 6 months data (2 lots) are available

for GAMMAGARD LIQUID conformance lots. For all conformance lots, the values for stability attributes remained within the preset specifications after storage at +5°C and +25°C for the period of observation. The studies are ongoing. The current studies support a shelf-life of 36 months at +5°C (+2 to +8°C), and 9 months maximum storage at +25°C within the first 24 months shelf-life of the product.

E. Labeling

The labeling consists of a package insert (full prescribing information), vial labels and unit cartons. The package insert, container and package labels are in compliance with 21 CFR 201 Subparts A and B and 21 CFR § 610.60, § 610.61 and § 610.62. The trade name, GAMMAGARD LIQUID, is not known to be in conflict with or easily confused with the trademark of any other licensed pharmaceutical product.

F. Establishment Inspections

GAMMAGARD LIQUID will be manufactured at Baxter facilities located in Los Angeles, California, Vienna, Austria and Lessines, Belgium. The Pre-approval Inspections of the Los Angeles and Vienna facilities were waived. The Lessines, Belgium facility was inspected from 12-20 January 2005. A Form FDA 483 was issued at the Lessines, Belgium facility. The issues were addressed accordingly. These three establishments have been found to be in compliance with current Good Manufacturing Practices.

5.0 PHARMACOLOGY AND TOXICOLOGY

The overall testing strategy was to compare the new product with a licensed immunoglobulin for intravenous infusion, Gammagard S/D, in most of the non-clinical studies. Non-clinical testing focused on potency, safety, pharmacokinetics, toxicity and mutagenicity.

A. Pharmacology

Potency: The potency of GAMMAGARD LIQUID for *in vivo* protective activity against virulent, mouse-lethal, human pathogens was assessed by a "mouse protection test" *in vivo*. Eighteen to twenty hours after intravenous administration of GAMMAGARD LIQUID or GAMMAGARD S/D mice were challenged intraperitoneally with bacterial cultures of *Streptococcus pneumoniae* or *Klebsiella pneumoniae*. Mortality rates were assessed for 14 days and the estimated median lethal dose of each challenge organism in mice after treatment with either GAMMAGARD LIQUID or GAMMAGARD S/D was computed. GAMMAGARD LIQUID was equivalent or superior to GAMMAGARD S/D in *in vivo* protection against systemic bacterial infections under the conditions tested.

Further evidence for potency of the product was presented using *in vitro* testings. ----------
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----------. The ability of GAMMAGARD LIQUID ----------
---------- was comparable to GAMMAGARD S/D.

Safety: The effect of GAMMAGARD LIQUID on safety parameters was assessed by a series of studies with animal models.

Anaphylactoid potential after intra-arterial injection of 1000 mg/kg of GAMMAGARD LIQUID was investigated in spontaneously hypertensive rats (blood-pressure lowering effect) and in guinea pigs (bronchospastic effect). Fewer (in hypertensive rats) and no (in guinea pigs) anaphylactoid reactions were observed with GAMMAGARD LIQUID compared with GAMMAGARD S/D.

Thrombogenicity of GAMMAGARD LIQUID was assessed in a rabbit model (----------); intravenous administration of 500 mg/kg GAMMAGARD LIQUID was less thrombogenic than GAMMAGARD S/D.

Influence on vital functions (cardiovascular, respiratory) and disseminated intravascular coagulation parameters were tested in dogs. Dogs were intravenously infused with 500 mg/kg of GAMMAGARD LIQUID. GAMMAGARD LIQUID showed the same or better safety profile than GAMMAGARD S/D.

Based on the results from these animal models, it can be anticipated that the risk of an anaphylactoid reaction or development of a disseminated intravascular coagulation after treatment with GAMMAGARD LIQUID is at least as rare as after treatment with GAMMAGARD S/D.

B. Pharmacokinetics

One study was performed to evaluate the variables "*in vivo* recovery" and "half-life" after a single intravenous dose of 1000 mg/kg GAMMAGARD LIQUID or GAMMAGARD S/D. There were no statistically significant differences in the pharmacokinetic profile of GAMMAGARD LIQUID and GAMMAGARD S/D in rats.

C. Toxicology

Toxicity was tested in single-dose studies using mice (2500, 5000 and 10000 mg/kg i.v.) and rats (limit test; 2000 mg/kg i.v.). The “No Observed Adverse Effect Level” for GAMMAGARD LIQUID was 5000 mg/kg in mice and 2000 mg/kg in rats. Based on these results it can be concluded that the toxicological profile of GAMMAGARD LIQUID in mice and rats is comparable to that of GAMMAGARD S/D.

Local tolerance was assessed in a study in rabbits after intravenous, intra-arterial or paravenous administration of GAMMAGARD LIQUID or GAMMAGARD S/D. Local tolerance was comparable for both immunoglobulin preparations.

Mutagenicity data, although not necessarily needed for plasma-derived products, was generated in bacteria (Ames test). A classic Ames test was performed for one lot of GAMMAGARD LIQUID and revealed non-mutagenicity under the conditions tested.

6.0 CLINICAL

The clinical study 160101 was designed to evaluate the pharmacokinetics, efficacy and safety of GAMMAGARD LIQUID in patients suffering from primary immunodeficiency diseases. Sixty-one subjects received a dose of 300-600 mg/kg every 21 to 28 days. Subjects in this study were treated for at least 12 months with a median weight-adjusted dose of 455 mg/kg. The 61 subjects in this study were between 6 to 72 years of age, 54% female and 46% male, and 93% Caucasian, 5% African-American, and 2% Asian.

A. Efficacy

The primary efficacy endpoint was the annualized rate of acute serious bacterial infections, i.e., the mean number of specified acute serious bacterial infections per subject per year. Specified acute serious bacterial infections were to meet specific diagnostic requirements (i.e. were validated). Per definition specified acute serious bacterial infections comprised bacteremia/sepsis, bacterial meningitis, osteomyelitis / septic arthritis, bacterial pneumonia and visceral abscess.

There were no specified acute serious bacterial infections in any of the 61 treated subjects. The annualized rate of specified acute serious bacterial infections was significantly less ($p < 0.0001$) than the rate of 1 infection per year. Thus, this study met the primary efficacy objective.

The secondary efficacy endpoints in this study were the annualized rate of validated other specified bacterial infections commonly occurring in primary immunodeficient subjects (urinary tract infections, gastroenteritis, lower respiratory tract infection (excluding pneumonia) and otitis media), and the number of hospitalizations secondary to these validated infectious complications. There were 4 of these other specified bacterial infections commonly occurring in primary immunodeficient subjects; none were serious or severe, and none resulted in hospitalization. These comprised 1 case of urinary tract infection, 1 case of gastroenteritis, and 2 cases of otitis media. All 4 of these infections resolved completely. The mean rate of these other specified bacterial infections commonly occurring in primary immunodeficient subjects was 0.07 per subject per year.

The mean rate of all clinically-defined but non-validated infections was 3.4 infections per patient per year. These consisted primarily of recurrent episodes of commonly observed infections in this patient population, those occurring in >5% of subjects are listed in Table 3.

Table 3
Commonly Observed Infectins Occurring in
> 5% of Subjects

Infections	**Percent of Subjects**
Sinusitis	57.4
Nasopharyngitis	24.6
Bronchitis	18.0
Upper respiratory infections	18.0
Urinary tract infections	8.2

B. Pharmacokinetics

To avoid carry-over effects of previously used IGIV products, the pharmacokinetic parameters of GAMMAGARD LIQUID were evaluated after 4 consecutive infusions of study product. Blood was drawn for evaluation of serum total IgG levels at pre-infusion, 30 minutes, and 1, 4, 10, 14, and 21 to 28 days after the infusion. All pharmacokinetic calculations were done using serum total IgG values at each post-infusion time-point. Fifty-seven subjects were included in the pharmacokinetic dataset.

Median total IgG decreased from 2040 mg/dL at 30 minutes after the infusion to 1040 mg/dL 21 to 28 days after the infusion. Area-under-the-curve ($AUC_{0\text{-}21d}$) was calculated from pre-infusion to 21 days post-infusion. Median values for $AUC_{0\text{-}21d}$ were 29139 mg·days/dL overall. The overall median value for elimination half-life was 35 days. Median *in-vivo* recovery was 112% and median incremental recovery was 2.3 (mg/dL)/(mg/kg). The formula to calculate *in-vivo* recovery included the plasma volume, which was estimated from body weight and hematocrit, but did not include other parameters known to affect plasma volume. This may lead to an inherent inaccuracy in the determination of the *in-vivo* recovery, which may account for the *in-vivo* recovery being greater than 100% of the dose administered.

Total IgG trough levels were determined at baseline and prior to each infusion to ensure adequate dosing of GAMMAGARD LIQUID, i.e. to maintain total IgG trough levels above 450 mg/dL. Median total IgG trough levels varied from 960 to 1120 mg/dL prior to each infusion during the efficacy period.

C. Safety

A total of 826 infusions of GAMMAGARD LIQUID were administered, with a median number of 13 infusions per subject. The median total exposure per subject over the course of the study was 436.3 g. The median weight-adjusted dose per subject per infusion was 455 mg/kg.

Adverse experiences were examined among a total of 61 enrolled subjects with primary immunodeficiency who received at least one infusion of GAMMAGARD LIQUID. For this study, temporally associated adverse events are defined as those occurring during or within 72 hours of completion of an infusion.

Of all adverse experiences, 15 events in 8 subjects were serious. Two serious events, two episodes of aseptic meningitis in one patient, were deemed to be possibly related to the infusion of GAMMAGARD LIQUID.

Among the 896 non-serious adverse experiences, 258 were reported as being possibly or probably related to the infusion of GAMMAGARD LIQUID. Of these, 136 were mild, 106 were moderate, and 16 were severe.

A total of 14 hospitalizations occurred during the study; none were related to infections.

A total of 345 temporally related adverse experiences were reported. These experiences were associated with 24.94% of infusions, significantly less ($p < 0.0001$) than the hypothesized incidence rate of 40%. Thus, the study met its primary safety objective.

Of these temporally related adverse experiences, those occurring in > 5% of subjects are shown in Table 4.

Table 4 Adverse Events*, Regardless of Causality, That Occurred within 72 Hours of Infusion in >5% of Subjects				
Event	**By Infusion**		**By Subject**	
	Number	**Percentage**	**Number**	**Percentage**
Headache	57	6.90	22	36.1
Fever	19	2.30	13	21.3
Fatigue	18	2.18	10	16.4
Vomiting	10	1.21	9	14.8
Chills	14	1.69	8	13.1
Infusion site events	8	0.97	8	13.1
Nausea	9	1.09	6	9.8
Dizziness	7	0.85	6	9.8
Pain in Extremity	7	0.85	5	8.2
Diarrhea	7	0.85	5	8.2
Cough	5	0.61	5	8.2
Pruritus	5	0.61	4	6.6
Pharyngeal Pain	5	0.61	4	6.6

* Excluding Infections

Of these events, only headache occurred in association with more than 5% of infusions.

Hematology and clinical chemistry parameters were monitored in all subjects prior to each infusion and throughout the 12-month period of study. Mean values for all laboratory parameters remained consistent throughout the study period. Three of the hematology values in one subject were outside of the normal range and reported as non-serious adverse experiences that resolved completely. These were a red cell count of 3.9 $x10^6/\mu L$, hematocrit of 31%, and white cell count of 3.88 x $10^3/\mu L$. All spontaneously returned to baseline. One subject had an elevated BUN (45 mg/dL) and creatinine (1.4 mg/dL) on one occasion that were reported as non-serious adverse experiences and resolved completely. These values improved to 30 mg/dL and 0.8 mg/dL, respectively, by the next infusion. Six of the patients had a single, transient elevation in serum transaminases. Two patients had persistent elevations in transaminases, ALT and AST, which were present at the initiation of the study, prior to the infusion of GAMMAGARD LIQUID. There was no other evidence of liver abnormalities. None of the hematology or chemistry laboratory abnormalities that occurred during the course of the study required clinical intervention and none had clinical consequences.

During the Phase 3 clinical study, viral safety was assessed by serological screening for HBsAg and antibodies to HCV and HIV-1 and HIV-2 prior to, during, and at the end of the study and by Polymerase Chain Reaction (PCR) tests for HBV, HCV, and HIV-1 genomic sequences prior to and at the end of the study. None of the 61 treated subjects were positive prior to study entry and none converted from negative to positive during the 12-month period of study.